although only 9 of their 40 reported cases would have been included in our group. Of the 14 deaths three were from causes other than asphyxia, and two more—a therapeutic abortion and another with a gross congenital abnormality—would very probably have occurred whatever methods were employed. Of the remaining nine fatal cases, seven responded initially to insufflation, although they died later after periods ranging from five hours to four days with varying degrees of atelectasis and evidence of amniotic aspiration. Of the two who failed to respond, one was a very small premature infant and the other was the only case to show a mild degree of subpleural emphysema.

We have in addition tried to obtain information on precisely how insufflation may modify the physical state of the lungs. The rapid oxygenation of the asphyxiated, as shown by skin colour, the movement of the chest wall, and the showers of fine crepitations on auscultation at each insufflation, suggested that the alveoli themselves were being expanded. Unfortunately, we were not able to obtain any radiographic records in the labour wards; a number of photographs, however, were obtained very shortly after death. Two of these are shown (Figs. 1 and 2), and they suggest that a pressure of +20 cm. of saline is sufficient to produce a considerable degree of alveolar expansion whilst it is exerted.

FIG. 1.—Case H. Birth weight 4 lb. (1.8 kg.). Control picture showing extensive atelectasis.

FIG. 2.—Same infant as in Fig. 1, showing alveolar expansion with a sustained intratracheal pressure of +20 cm. of saline.

In addition we have practised this technique in eight very small premature infants who appeared to be dying as a result of atelectasis, in one case continuing for eight hours. In all these there was a transient recovery, as evinced by a rise in pulse rate and improved colour. Life never seemed to be prolonged more than a few hours, and the manipula-

tions of inserting the tube and changing it when blocked with mucus were badly tolerated. Extensive atelectasis without emphysema was revealed in all cases at necropsy. This information, together with that from the post-mortem reports of babies dying of asphyxia, suggests that endotracheal insufflation with the pressures we have used does not to any perceptible degree facilitate the permanent expansion of the atelectatic lung in the newborn, although it may do so in some dead or stillborn infants, especially if full-term. A satisfactory degree of oxygenation of the blood and tissues can, however, be produced almost immediately.

Finally, we would stress the desirability of an established routine in the treatment of asphyxiated infants. For convenience this may be primarily but not exclusively the responsibility of the anaesthetist, the obstetrician, or the paediatrician. To ensure prompt action in the unexpected emergency all should be proficient in the technique employed.

Conclusions

The administration of oxygen under intermittent positive pressure of up to +20 cm. of water by endotracheal tube is, in experienced hands, a safe, quick, simple, and efficient treatment for severe cases of asphyxia neonatorum.

This procedure, though momentarily expanding the alveoli, does not appear permanently to modify the physical state of the unexpanded newborn lung.

We would like to thank Professor J. C. McClure Browne and Professor A. A. Moncrieff for permission to carry out these investigations on infants under their care, and also Dr. C. Upjohn and Dr. M. W. Arthurton, who intubated many of these babies and assisted in keeping the records. Dr. B. W. Powell, Assistant to the Professor of Child Health, kindly reassessed the developmental age of two infants.

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THE RESPIRATORY EFFECTS OF SALICYLATE

BY

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There is an extensive literature on the effect of salicylates on respiration and on the acid-base balance of the blood. Most observers agree that salicylate causes hyperventilation and a reduction in the carbon dioxide content of the blood. There has been great controversy, with many conflicting reports on the interpretation of these findings: whether salicylate causes a primary respiratory alkalosis or a metabolic acidosis with secondary hyperventilation (Johnson, 1930; Morris and Graham, 1931; Rapoport and Guest, 1945; Reid, Watson, and Sproull, 1950).

It was decided to investigate the respiratory effects of orally and intravenously administered salicylate in the human subject. For this purpose a closed-circuit Knipping type spirometer was used. This apparatus measures oxygen consumption, carbon dioxide output, and depth and rate of respiration. Most previous observations on the effect of salicylates on the respiratory movements in the human subject have been made

by clinical assessment, and it was thought that a spirometer record might be of value in defining this effect more accurately and at the same time enable the respiratory gaseous exchanges to be studied.

Method

The Knipping spirometer is a modification of the ordinary Benedict-Roth type, so that it is possible to show on the same record the volume of CO₂ produced as well as the volume of O₂ consumed. By using a rotary airpump to ventilate the apparatus no valves are necessary. Included in the circuit is a special flask which holds potassium hydroxide solution to absorb CO₂. At the top of the flask is a container for sulphuric acid, which is released through a stop-cock when it is desired to ascertain the CO₂ produced. It was found at first that CO₂ tended to accumulate in the apparatus, and this resulted in hyperventilation. By trial and error the optimal conditions for satisfactory absorption of circulating CO₂ were established. For a 10-minute spirometer tracing a relatively fast pump-speed of about 870 r.p.m. and 150 ml. of 2.5/N KOH solution are required. The output of air by the pump at this speed is about 33 litres a minute, and to prevent leaks the mouthpiece and nose-plug must be carefully and securely fitted.

Experiments were carried out on five healthy young adult male volunteers and on four patients, three with subacute rheumatism and one with rheumatoid arthritis in a quiescent state.

The healthy subjects and the rheumatoid patient came into hospital the night before the experiment, and in the morning were given a standard breakfast of a cup of tea and a slice of toast. In two of the healthy subjects and in the rheumatoid patient two or three control 10-minute spirometer tracings were recorded, and then an intravenous drip of sodium

salicylate (10 g. in 400 ml. of distilled water) was given over a period of three to four hours. During the intravenous drip, at approximately half-hour intervals, 10-minute spirometer tracings were taken. The remaining three healthy subjects served as controls. They were given no intravenous drip, but in every other respect were treated like those who received salicylate.

The three subacute rheumatic patients had been sent into hospital as cases of rheumatic fever. On admission they were found to be afebrile and free from carditis, and the only abnormal finding was pain on movement of one or two joints. They were confined to bed and received a standard breakfast. Each morning at a constant time three consecutive five-minute spirometer tracings were taken and the results averaged. When a satisfactory baseline had been obtained oral treatment with aspirin was started in doses of 1½–2 g. five times a day, and morning tracings were continued until treatment was stopped and the respiratory changes returned to the previous control values.

In all subjects occasional blood samples were taken for plasma salicylate determinations.

Results

In the three healthy subjects who acted as controls for the intravenous salicylate experiment it was found that the oxygen consumption and carbon dioxide output remained fairly constant throughout the day (Table I). In each subject there were variations in O₂ consumption and CO₂ output of 20–40 c.cm. a minute, and the respiratory quotients varied by 0.05–0.15. However, no definite sequence of changes was observed, and it was clear that serial tracings at approximately half-hour intervals did not increase O₂ consumption or CO₂ output, and depth and rate of respiration remained constant within narrow limits.

TABLE I.—Serial Spirometer Results at Half-hourly Intervals Throughout a Four- to Five-hour Period in Three Healthy Young Adults

30-min. Intervals (approx.)	A. S.					A. R.					I. McD.				
	O ₂ c.cm./ min.	CO ₂ c.cm./ min.	R.Q.	Tidal Air c.cm.	Resp. Rate /min.	O ₂ c.cm./ min.	CO ₂ c.cm./ min.	R.Q.	Tidal Air c.cm.	Resp. Rate /min.	O ₂ c.cm./ min.	CO ₂ c.cm./ min.	R.Q.	Tidal Air c.cm.	Resp. Rate /min.
1	333	247	0.74	600	16	288	252	0.88	850	9	330	265	0.80	810	12
2	300	240	0.80	550	17	275	249	0.90	630	13	297	260	0.88	830	9
3	323	249	0.77	600	16	290	232	0.80	700	10	267	240	0.90	730	9
4	317	246	0.78	580	17	285	237	0.83	690	11	272	260	0.95	800	10
5	317	255	0.80	570	18	285	245	0.86	770	9	280	241	0.86	800	9
6	315	249	0.79	560	17	267	215	0.81	730	8	252	245	0.97	840	10
7	315	247	0.78	550	17	292	218	0.75	650	10	258	254	0.98	800	11
8	318	256	0.81	600	17	275	225	0.82	630	12	253	238	0.94	730	10
9											280	241	0.86	750	10
10											268	251	0.94	800	10

TABLE II.—Serial Spirometer Results in Two Healthy Adults and in One Rheumatoid Patient (R. A.) who Received Sodium Salicylate by Intravenous Drip

A. R.*						R. A.†						H. D.‡								
Time	O ₂ c.cm./ min.	CO ₂ c.cm./ min.	R.Q.	Tidal Air c.cm.	Resp. Rate /min.	Plasma Sal. mg./ 100 ml.	Time	O ₂ c.cm./ min.	CO ₂ c.cm./ min.	R.Q.	Tidal Air c.cm.	Resp. Rate /min.	Plasma Sal. mg./ 100 ml.	Time	O ₂ c.cm./ min.	CO ₂ c.cm./ min.	R.Q.	Tidal Air c.cm.	Resp. Rate /min.	Plasma Sal. mg./ 100 ml.
a.m.							a.m.							a.m.						
9.14	313	248	0.79	730	11		9.44	258	222	0.86	630	14		9.27	270	236	0.87	550	14	
9.34	322	231	0.72	700	10		10.4	267	230	0.86	600	14		9.48	283	256	0.90	630	13	
9.52	312	248	0.79	800	9		10.24	248	228	0.92	660	15		Means	277	246	0.89	590	14	
Means	316	242	0.77	740	10		Means	258	227	0.88	630	14		10.57	337	287	0.85	710	16	
10.56	310	247	0.80	780	11		11.29	267	244	0.91	780	16		11.21	362	280	0.77	650	16	
11.33	318	257	0.81	720	11		11.59	292	256	0.88	740	16		11.43	382	278	0.73	710	16	
11.52	335	255	0.76	700	14		p.m.							p.m.						
12.23	377	265	0.70	750	12	22.5	12.35	295	263	0.89	890	16		12.20	418	295	0.71	610	20	18
1.15	429	322	0.75	890	15		1.15	322	273	0.85	850	18		1.15	480	325	0.68	760	19	27
2.0	460	316	0.69	900	14		1.48	368	272	0.74	880	15		2.0	467	303	0.65	650	20	
2.25	502	363	0.72	1,100	15	38.0	2.17	372	268	0.72	1,080	16		2.28	445	310	0.70	720	19	
3.10	467	312	0.67	1,070	12		2.35	422			1,050	17	63	3.36	447	300	0.67	680	19	
3.40	497	321	0.65	1,100	12															
4.48	453	301	0.65	950	12															

* From 10.56 a.m. to 2.25 p.m. Case A. R. received 8 g. of salicylate in 325 ml. of distilled water intravenously.

† From 11.29 a.m. to 2.35 p.m. Case R. A. received 10 g. of salicylate in 400 ml. of distilled water intravenously.

‡ From 10.57 a.m. to 1.15 p.m. Case H. D. received 7.5 g. of salicylate in 300 ml. of distilled water intravenously.

TABLE III.—Daily Spirometer Results in Three Patients with Subacute Rheumatism who Received Aspirin by Mouth

J. McL.*							B. E.†							J. McM. ‡						
Day	O ₂ c.cm./ min.	CO ₂ c.cm./ min.	R.Q.	Tidal Air c.cm.	Resp. Rate /min.	Plasma Sal. mg./ 100 ml.	Day	O ₂ c.cm./ min.	CO ₂ c.cm./ min.	R.Q.	Tidal Air c.cm.	Resp. Rate /min.	Plasma Sal. mg./ 100 ml.	Day	O ₂ c.cm./ min.	CO ₂ c.cm./ min.	R.Q.	Tidal Air c.cm.	Resp. Rate /min.	Plasma Sal. mg./ 100 ml.
1	242	192	0.79	400	24	40	1	228	219	0.95	360	21	25	1	282	242	0.86	490	21	42 49
2	237	177	0.75	380	22		2	228	205	0.90	390	20		2	251	244	0.96	480	23	
3	237	190	0.80	440	20		5	226	203	0.90				3	266	266	1.0	590	21	
6	227	191	0.84	450	21		6	224	199	0.89	390	22		4	270	277	1.0	610	22	
7	223	185	0.83	470	20		Means	227	207	0.91	380	21		5	257	234	0.94	500	23	
Means	233	187	0.80	430	21		7	236	223	0.94	470	21		6	275	259	0.93	540	20	
8	237	200	0.84	590	19		8	245	221	0.90	500	19		8	294	283	0.97	560	19	
9	279	211	0.76	650	20		9	262	208	0.80	490	18		9	289	281	0.97	630	19	
10	276	218	0.79	830	19		12	233	197	0.86	420	18		Means	273	260	0.95	550	21	
13	317	209	0.66	940	21		13	222	192	0.87	420	16		10	297	280	0.94	750	16	
14	260	214	0.82	770	19		14	246	214	0.88	440	18		11	345	307	0.89	930	17	
15	209	187	0.89	540	18		15	230	202	0.88	440	18		12	386	309	0.80	1,000	16	
16	199	180	0.91	510	17	16	221	190	0.86	390	18	13	300	267	0.89	760	13			
17	208	173	0.84	500	15	19	220	202	0.90	410	18	15	265	251	0.94	650	13			
20	195	172	0.88	460	17							16	269	245	0.91	620	15			
21	209	188	0.90	480	15															

* From the eighth to the thirteenth day Case J. McL. received 37.5 g. of aspirin orally.

† During the seventh and eighth days Case B. E. received 21 g. of aspirin orally.

‡ During the tenth and eleventh days Case J. McM. received 26 g. of aspirin orally.

Table II shows the results obtained in the two healthy young adult male subjects (A. R. and H. D.) and in the rheumatoid arthritis patient (R. A.), who received sodium salicylate by intravenous drip. The initial control readings are averaged, and these values can be compared with those obtained during and after the intravenous drip. There is a progressive and marked increase in O₂ consumption. When the average value for the control period is compared with the maximum value obtained during the intravenous drip it will be seen that the increase in O₂ consumption per minute for subject A. R. is 186 c.cm. (59% increase), for R. A. 164 c.cm. (64% increase), and for H. D. 203 c.cm. (73% increase). In all subjects the increased O₂ consumption was accompanied by an increased CO₂ elimination, but a disproportion between the levels of O₂ and CO₂ developed, so that the respiratory quotients showed a progressive fall. In two subjects (A. R. and R. A.) the fall in R.Q. did not occur until the intravenous salicylate drip had been in progress for two to three hours, whereas in one subject (H. D.) the R.Q. showed a significant fall within one hour of starting the drip. Hyperventilation was observed in all three subjects. In two (A. R. and R. A.) the tidal air at the time

of maximal O₂ consumption had increased from the average control value by 360 and 420 c.cm. respectively, while in subject H. D. hyperventilation was less marked throughout the experiment, and the maximal tidal air was only 170 c.cm. greater than the average control value. In each subject salicylate caused an increase in the rate of respiration, by about four to six respirations a minute. The greatest augmentation of respiratory rate occurred in the subject (H. D.), who showed the smallest increase in tidal air. The results in one subject (A. R.) are shown in graphic form in Fig. 1.

A similar pattern of changes was observed in the three patients who received aspirin by mouth (Table III). The overall increase in O₂ consumption was not so great as in the intravenous experiments. The maximal O₂ consumption exceeded the average control value in patient J. McL. by 84 c.cm. (36% increase), in B. E. by 35 c.cm. (15% increase), and in J. McM. by 113 c.cm. a minute (41% increase). As before, the increase in CO₂ output was not proportional, and this resulted in a fall in R.Q. which was not manifest until the second or third day of treatment. Hyperventilation occurred in all patients within 24 hours of starting treatment, and in two of the patients (J. McL. and J. McM.) the maximal tidal air was approximately double the average control value. The respiratory rate was either unaltered or showed a slight reduction. Fig. 2 illustrates the changes in one patient.

It will be seen in Figs. 1 and 2 that there is a definite parallelism between the curves of O₂ consumption and tidal air. To eliminate the possibility that deep breathing on the spirometer might potentiate an O₂ leak and thereby cause an apparent increase in O₂ consumption, the effect of voluntary hyperpnoea was compared with normal respiration in two of the subjects who had been used for the oral aspirin experiments. The expected increased elimination of CO₂ was observed, but no increase in O₂ consumption occurred even when the tidal air was almost doubled (Fig. 3).

FIG. 1.—A graphic record of the results obtained in one subject (A. R.) who received sodium salicylate by intravenous drip. There is a progressive rise in O₂ consumption and tidal air during the intravenous drip. The respiratory quotient falls owing to a disproportionate rise in CO₂ output.

FIG. 2.—A graphic record of the results obtained in one patient (J. McL.) who received oral aspirin treatment. Increased O₂ consumption and tidal air due to aspirin are clearly seen. The rise in CO₂ output is disproportionate and the R.Q. falls.

Discussion

Barbour and Devenis (1919), using a Benedict respiration chamber, showed that aspirin in single doses of 1 g. orally caused a slight increase in metabolism (6.1%) in normal individuals. They also observed a slight increase in CO₂ output, but no alteration in respiratory quotient. In the present investigation there is a marked and progressive increase in O₂ consumption when salicylate is given in full therapeutic

dosage to normal and subacute rheumatic subjects.

In the investigations described the maximal increase in O₂ consumption was 30–40% for oral aspirin and 60–70% for intravenous salicylate. In the oral experiments the aspirin dosage and the plasma salicylate levels at the times of maximal O₂ consumption are within ordinary therapeutic limits. In the intravenous experiments the dosage of sodium salicylate used (10 g. in 400 ml. of distilled water in three to four hours) is a little higher than that

recommended by Coburn (1943) in the treatment of the active phase of rheumatic fever (10 g. of sodium salicylate in 1,000 ml. of 0.9% NaCl in four to six hours), but again the plasma salicylate levels at the times of maximal O₂ consumption are within ordinary therapeutic limits in two subjects. In the third subject (R. A.) a plasma salicylate level of 63 mg. per 100 ml. occurred at the height of O₂ consumption, and was associated with excessive restlessness, confusion, and nausea. This was the only occasion in the whole of the investigations when toxic effects caused some anxiety. It is noteworthy that increased O₂ consumption occurred early in both oral and intravenous experiments—in the former within 24 hours, in the latter within half to one hour of starting treatment. Insufficient plasma salicylate estimations were done to determine at what level O₂ consumption increased, but in three subjects a definite increase had occurred at levels of 20–30 mg. per 100 ml.

The increased O₂ consumption following salicylate must be due to an increased metabolic rate. As regards the particular metabolite or metabolites affected, the observed fall in R.Q. would suggest that protein and/or fat is being predominantly combusted. In each subject studied the R.Q. showed a progressive fall during the period of salicylate therapy and reached its lowest level about the time of maximal oxygen consumption. There are numerous reports in the literature concerning the effect of salicylate on carbohydrate and protein metabolism. Hyperglycaemia and glycosuria have often been described in cases of salicylate poisoning, and Morris and Graham (1931), from a study of the effect of salicylate in the fasting blood-sugar level in rheumatic children, conclude that the drug inhibits the utilization of glucose by the tissues. Much of the work on protein metabolism has concerned the stimulation of uric acid excretion, but Reid, Watson, and Sproull (1950), from a study of the nitrogen balance in rheumatic patients treated with salicylate, conclude that an important therapeutic action of the drug is to stimulate protein catabolism. The effect on fat metabolism has so far been neglected.

From the present investigation no definite conclusions can be drawn concerning the nature of the metabolic stimulation, and further study is required in both the normal and the rheumatic subject. It is nevertheless believed that the marked and progressive increase in tissue oxidation following salicylate treatment may well be of fundamental importance in the therapeutic action of the drug.

Summary

The effect of orally and intravenously administered salicylate on respiration in the human subject has been studied by means of a Knipping type closed circuit spirometer. In addition to an increase in depth of respiration, the drug caused a marked and progressive increase in O₂ consumption. It is suggested that this latter effect may be of fundamental importance in the therapeutic action of the drug.

I thank Professor Sir John McNee for his advice and generous help in providing facilities for this work. I am greatly indebted to Dr. James Reid and Dr. David Sproull for their criticism and technical assistance throughout the investigations.

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FIG. 3.—The effect of voluntary deep breathing on O₂ consumption and CO₂ elimination in one of the patients (J. McL.) who was used in an oral aspirin experiment. Although the tidal air has been almost doubled there is no increased consumption of O₂. The expected increased elimination of CO₂ occurred.

Witch-doctors in South Africa are no longer to be allowed to advertise their magic remedies, according to a report in *The Times* (October 25). The advertisement of medicines containing human ingredients, insects and reptiles, "super-natural legendary and mythical beings," and substances giving protection against "hostile agencies, supernatural powers, witchcraft, or unnatural diseases," will make the practitioner concerned liable to a fine of £50 and six months in prison.